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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,008	05/06/2002	Steven K Libutti	14014.0322U2	3848

36339 7590 11/09/2006

NATIONAL INSTITUTE OF HEALTH
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ATLANTA, GA 30303

EXAMINER

BURKHART, MICHAEL D

ART UNIT	PAPER NUMBER
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1633

DATE MAILED: 11/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/031,008

Applicant(s)

LIBUTTI ET AL.

Examiner

Michael D. Burkhardt

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 August 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19, 21-37, 39 and 40 is/are pending in the application.
- 4a) Of the above claim(s) 3, 5-15, 17, 19, 23-37 and 39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 4, 16, 18, 21, 22, and 40 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

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DETAILED ACTION

Receipt and entry of the amendment dated 8/28/2006 is acknowledged. After entry of the amendment, claims 1-19, 21-37, 39 and 40 are pending. Claims 3, 5-15, 17, 19, 23-37 and 39 remain withdrawn as directed to non-elected inventions. Claims 1, 2, 4, 16, 18, 21, 22, and 40 are under examination.

Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, 18, 21 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Restifo et al (U.S. patent 5,733,548, of record) as evidenced by Tandle et al (J. Trans. Med., of record). **This rejection is maintained for reasons made of record in the prior Office Action and for reasons set forth below.**

Response to Arguments

Applicant's arguments filed 8/28/2006 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) Restifo et al use small peptides fused to the adenoviral E3 signal sequence as immunogens, which peptides indirectly lyse tumor cells via T cell activation. Thus, such proteins would not be recognized by one of skill in the art as antiangiogenic; 2) none of the angiogenesis inhibitors taught by Tandle et al inhibit angiogenesis by T cell activation, thus none of the inhibitors taught by Tandle et al are analogous to the E19/P1A fusion protein of Restifo et al; 3) the Examiner is reminded that extrinsic evidence may be used to explain but not expand the meaning of terms used in an anticipation rejection.

Regarding 1), the instant application and Tandle et al teach no size limitations regarding what and what is not to be considered an antiangiogenic protein. The term "antiangiogenic protein" is extremely broad, and encompasses a broad genus of proteins with a wide range of structures, functions, and effects (see a limited list in Table I of Tandle et al). Furthermore, Tandle et al is not relied upon to teach a limitation of the instant claims (this also applies to 3) above), only to provide guidance for the interpretation of claim language. Hence, assertions that one of skill in the art would not recognize the E19/P1A protein of Restifo et al as "antiangiogenic" is of little probative value, absent evidence to the contrary. Regarding 2), one example of an indirect angiogenesis inhibitor is IL-12 (page 8, second column of Tandle et al) which inhibits angiogenesis through a complex series of mechanisms, one of which is the cytotoxic effects (i.e. lysis) of TNF and IFN- γ (produced by T cells) for tumor cells (Trinchieri, Nat. Rev. Immun., 2003, Box 4, page 143). Regarding 3), the term "antiangiogenic protein" is very broad, as evidenced by the wide range of proteins listed by Tandle et al as being antiangiogenic. Thus, Tandle et al has been used to explain the term, not expand it. The E19/P1A protein of Restifo is indeed a protein, and because of the indirect effects of this protein on angiogenesis, is considered antiangiogenic.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, 4, 16, 18, 21, 22 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al (U.S. patent 6,638,502) in view of Restifo et al (as above). **This**

rejection is maintained for reasons made of record in the prior Office Action and for reasons set forth below.

Response to Arguments

Applicant's arguments filed 8/28/2006 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) there is no motivation to combine the Restifo et al and Li et al references because of a difference in size and structure of the respective proteins taught by the references, thus they are not analogous art; 2) there would be no expectation of success when linking the E19 signal sequence to an antiangiogenic protein; 3) linking the E19 signal sequence to an antiangiogenic protein in the instant application produced the unexpected result of increasing circulating levels of the antiangiogenic protein, leading to the ability to treat tumors via systemic delivery, a property not found in the prior art.

Regarding 1), in response to applicant's argument that Restifo et al and Li et al are nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, both references involve the gene therapy of cancer by recombinant viruses. Thus, not only are they analogous to each other, they are analogous to the instant invention. Regarding 2), Restifo et al indicate the signal sequence may precede another peptide from 5 to 1000 amino acid residues (column 4, lines 32-40). Prior art is presumed to be enabling, absent evidence to the contrary, see MPEP 2121. Applicants present no reasoning or evidence as to why expression of a heterologous polypeptide using the E19 signal sequence as taught by Restifo et al would be

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unexpected. Indeed, the signal sequence naturally directs the expression of a 19 kD protein, (hence the name E19). Regarding 3), Li et al clearly teaches a signal sequence to direct the secretion of antiangiogenic proteins expressed from the adenoviral vectors (see the Examples), one of which, angiostatin, targets endothelial cells. Furthermore, the systemic administration of an adenovirus expressing plasminogen (secreted by the plasminogen leader sequence) delivered high levels of the protein and prevented tumor establishment and growth (Griscelli et al 1998, PNAS, see in particular page 6371, first column, first full ¶).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 40 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection necessitated by amendment of the claims.

Claim 40 recites the limitation "the angiogenic protein" in line 5. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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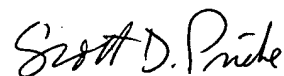
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael D. Burkhart
Examiner
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SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER